

Adult anaplastic pilocytic astrocytoma – a diagnostic challenge? A case series and literature review[☆]

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ABSTRACT

Introduction: Anaplastic pilocytic astrocytoma (APA) is an exceptionally rare type of high-grade glioma in adults. Establishing histopathological diagnosis is challenging and its clinical and radiological appearance insidious. By this case series and first literature review we investigated the various clinical, neuroradiological, and histopathological features of APA in adults.

Methods: An in hospital screening of the database from the Institute of Pathology was conducted to identify cases of APA. Further, we performed a literature review in PubMed using the keywords “anaplastic/malignant/atypical AND pilocytic astrocytoma” and “anaplastic astrocytoma/glioblastoma AND Rosenthal fibers” and summarized the current knowledge about APA in adults.

Results: Over the last decade we were able to identify 3 adult patients with APA in our hospital. According to the pertinent literature, the prognosis of APA in adults (documented survival of up to 10 years) appears to be better than in other high-grade gliomas. Few cases were associated with neurofibromatosis type 1, which seems to predispose for development of APA. Although molecular genetics is still of limited value for differentiation of APA from other high-grade glioma, advanced neuroimaging techniques such as magnetic resonance perfusion imaging and spectroscopy allow improved differential work-up. In particular, APA in adults has the ability to mimic various neurological diseases such as tumefactive demyelinating lesions, low-, or high-grade gliomas.

Conclusions: Although currently not explicitly recognized as a distinct clinico-pathologic entity it seems that adult APA behaves differently from conventional high-grade glioma and should be included in differential diagnostics to enable adequate patient care. However, further studies are needed to better understand this extremely rare disease.

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1. Introduction

Pilocytic astrocytoma (WHO grade I) is generally perceived as a relatively homogenous entity characterized by young patient age at presentation, a limited number of predilection sites (e.g., cerebellum, brain stem, hypothalamus, and optic nerve), a low risk of recurrence or progression after gross total resection, and characteristic histopathological features (including Rosenthal fibers and

a non-infiltrative growth pattern). However, very rarely tumors occur that resemble pilocytic astrocytoma, but show histological signs of anaplasia and follow an aggressive clinical course [1]. Such anaplastic pilocytic astrocytomas (APA) are particularly rare in patients older than 18 years of age [2].

Establishing a preoperative diagnosis of APA is challenging, as its clinical and radiological appearance is often unspecific. However, the clinical course of APA is perceived to be more favorable as compared to conventional anaplastic astrocytomas [3,4]. Here, we present 3 new cases with APA in adults diagnosed at our institution over the last decade and provide a first review of the current clinical, histopathological, and neuroradiological literature to update the reader's knowledge about APA.

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2. Methods

A screening of our in hospital database from the institute of Pathology was performed to identify adult patients with APA. The need for ethical approval was waived by the institutional review board due to sole case reporting setting of the study.

By the use of 5 different combinations of keywords “anaplastic/malignant/atypical AND pilocytic astrocytoma” and “anaplastic astrocytoma/glioblastoma AND Rosenthal fibers” in PubMed we obtained 207 different articles. Thereafter; we selected those reports with documented cases of APA in adult patients by screening the abstracts. The references in the relevant articles were also taken into consideration. All pediatric articles and those cases containing malignant transformation of adult pilocytic astrocytoma into anaplastic variants due to prior radio-/or chemotherapy were excluded from further investigations. In those articles with limited information about the type of neoplasm, we tried to contact the corresponding authors to obtain further details. Only reports in English language were considered for our investigation.

3. Results

3.1. Case series

The in hospital database screening led to the identification of 3 adult patients with APA (cases 1, 2, and 3):

3.1.1. Case 1

A 52-year-old man with a history of pelviglossectomy and bilateral neck dissection for squamous cell carcinoma of the oral cavity 2 years previously was admitted with a 4-week history of gait disturbance and memory deficits. Neurological examination revealed no further deficits. Neuroimaging showed an irregularly enhancing mass lesion of the left precuneus (Fig. 1A,D). Presumed preoperative diagnosis was a high-grade glioma. Gross total removal of the tumor was successfully accomplished at our institution in 2008. The histopathological work-up showed a cellular astrocytic neoplasm with mitotic activity, microvascular proliferation, and infarct-like necrosis, which was remarkable for the presence of bipolar tumor cells in a myxoid background. Furthermore, occasional eosinophilic granular bodies and rare Rosenthal fibers were observed (Fig. 2D,E). Tumor cells were negative for R132H-mutant IDH1. Based on these findings, a diagnosis of APA was issued. After the operation the patient underwent fractionated stereotactic radiation therapy (6×5 Gy). 19 months later he presented with tumor recurrence with infiltration of the corpus callosum, which was considered non-resectable and without further alternative treatment options due to the patient's poor clinical state. Unfortunately, the patient died 3 months later, after a documented survival of 22 months.

3.1.2. Case 2

A 41-year-old male was referred with a 6-week history of double vision, left facial paresthesia, and weakness of the left limbs. Clinical examination showed left abducens and facial nerve paresis. Magnetic resonance imaging (MRI) demonstrated an irregularly enhancing tumor of the right pons, suggesting either inflammation or malignancy (Fig. 1B,E). Stereotactic biopsy was conducted in 2009. Histologically, astrocytic cells with plump bipolar processes and rare Rosenthal fibers characterized the tumor (Fig. 2F). However, there was an elevated Ki-67 proliferation index ranging between 5 and 10% and nuclear p53 accumulation, but there was no immunoreactivity for R132H-mutant IDH1. The tumor was classified as APA. For further treatment, the patient received fractionated radiation therapy (total dose of 54 Gy). The patient did not

appear for regular follow-up appointments after completion of the 3-month long radiation therapy.

3.1.3. Case 3

A 60-year-old woman with known neurofibromatosis (NF) type 1 presented with visual disturbances, dizziness, and a change in mental state of 4-week duration. Further neurological status was normal. MRI showed a diffuse lesion in the thalamus, insula, and temporal white matter with indications of high-grade glioma, inflammation, or a metastatic lesion (Figs. 1C,F, 3 and 4). In 2009, a stereotactic biopsy was performed. The histological specimens revealed an astrocytic neoplasm characterized by the presence of Rosenthal fibers. While some of the fragments showed a low-grade component, others featured an elevated cellularity, consistent mitotic activity, glomeruloid microvascular proliferation, and nuclear p53 accumulation that qualified for classification as APA (Fig. 2A–C). Postoperatively, the patient was further treated by fractionated irradiation (30×2 Gy). Documented final follow-up was available 35 months after initial diagnosis.

3.2. Review of the literature

The literature review identified 20 articles (mostly single case reports) about anaplastic/malignant/atypical pilocytic astrocytoma or anaplastic astrocytoma/glioblastoma with Rosenthal fibers. By careful workup of these reports and exclusion of our 3 patients we obtained 31 cases of APA (Table 1). Notably, the cases described in Rodriguez et al., 2010 and 2011 (10 definitive APA cases) contained an unspecified number of subjects younger than 18 years of age (range 5–75 years) [1,5]. Historically, one of the first descriptions of APA in adults lasted back in the early nineties [6,7].

By systematic anatomical arrangement of the identified cases in Table 1, APA in adults seems to preferentially locate in the posterior cranial fossa. This is in contradiction to the common location of other types of high-grade glioma which mostly originate from the cerebral hemispheres.

In a study by Burkhard et al. 2 adult patients with APA provided documented long-term follow-ups of 7 and 10 years, respectively [4]. Similarly, we observed prolonged postoperative survival of up to 35 months in 1 of our patients (case 3). Compared to conventional anaplastic glioma the overall survival of adult patients diagnosed with APA appears to be improved.

New and advanced neuroimaging techniques such as MRI perfusion and spectroscopy allow improved differentiation between tumefactive demyelinating lesions, low-, and high-grade glioma which all can be mimicked by APA [8]. Typical imaging features of APA in adults are given in Figs. 3 and 4 (of case 3).

Finally, several cases of APA as well as 1 of our cases (case 3) were associated with NF type 1 which could predispose for this rare tumor entity [5,9].

4. Discussion

We report 3 new and remarkable cases of APA in adults with thorough diagnostic workup demonstrating the clinical, histopathological, and neuroradiological features relevant in diagnosis of this rare type of neoplasm. Moreover, our study presents one of the largest collections of APA in adult patients to date apart from an investigation that included various juvenile and adult cases of malignant transformation of pilocytic astrocytomas, NF-1 associated APA, and several histopathological occult cases [5,9]. In the literature, APA is frequently classified synonymously as anaplastic astrocytoma with abundant Rosenthal fibers, which includes uncommon and rare histologic features and was reported to occur in 5% of all patients diagnosed with pilocytic astrocytomas over a

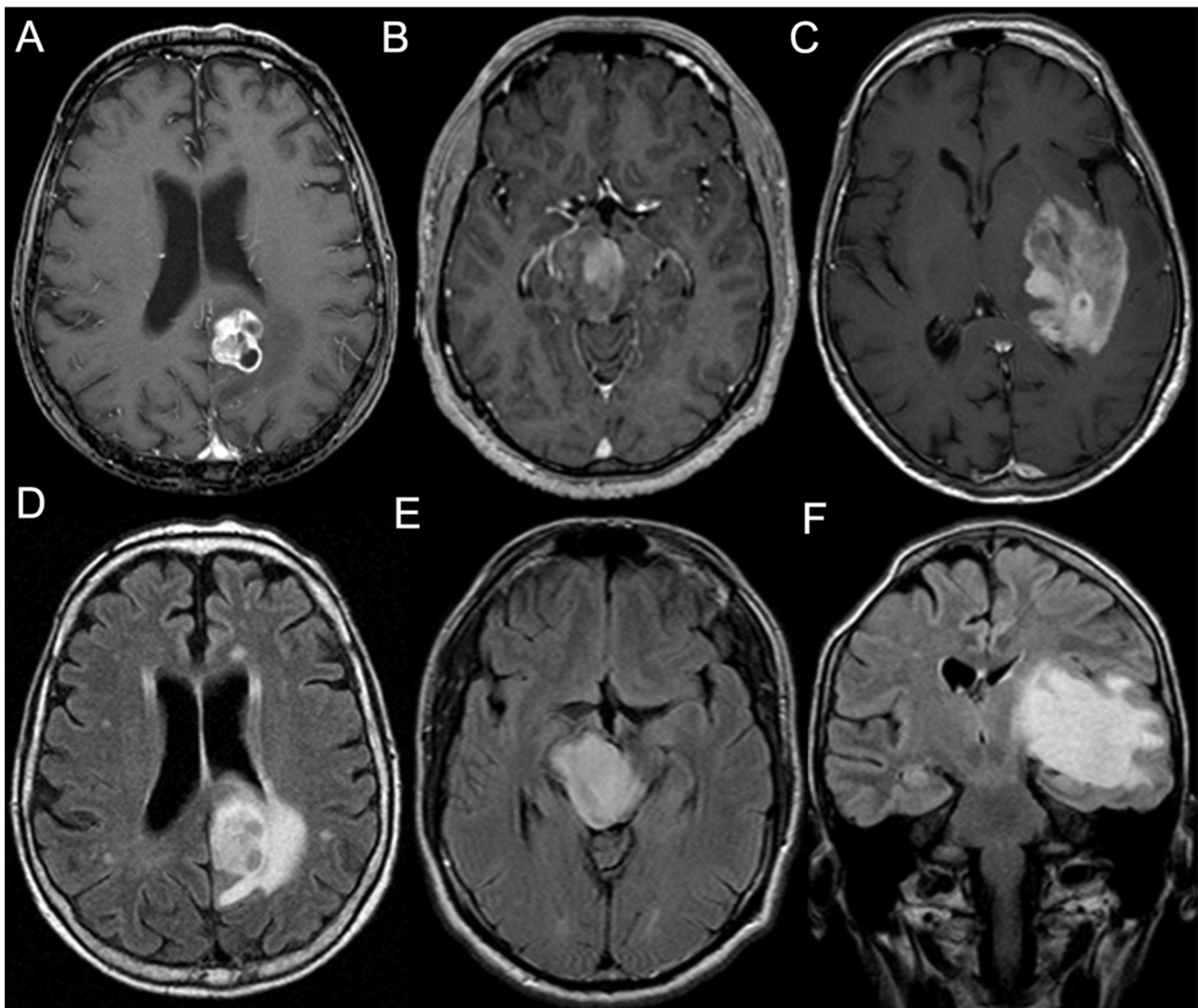


Fig. 1. Neuroimaging features of anaplastic pilocytic astrocytomas (APA). T₁-weighted gadolinium enhanced axial MRI slices (upper row) and axial or coronal FLAIR sequences (lower row) of cases 1–3: APA presenting as irregularly enhancing mass lesions in the left precuneus (A,D), the pons (B,E), and diffusely in the thalamus, insula, and temporal white matter (C,F). Note the variable appearance mimicking high-grade glioma in case 1 (A,D), tumefactive demyelinating lesion in case 2 (B,E), and a solid homogeneous mass appearing as a metastatic lesion in case 3 (C,F).

10-year observation period [10]. A recent study observed anaplastic features in APA in 2 of 25 cases over a 10-year period [11]. The incidence of pilocytic astrocytoma (4.8/1,000,000 patients per year) in combination with only 2 reported patients with adult APA (excluding 1 case arisen from malignant transformation after radiotherapy) in a study from Theeler et al. (127 patients with adult pilocytic astrocytoma) categorizes pilocytic astrocytoma with anaplastic features in adults as an extremely rare neoplasm [2,4].

4.1. Histopathological and genetic features

One of the first descriptions of APA in adults appeared in a publication from Hitotsumatsu et al. and Patt et al. in 1994, reporting on astrocytoma in the optic nerve [6,7]. The current diagnostic category of APA is based on the observation that such tumors may occur through progression from a conventional pilocytic astrocytoma associated with a low-grade component corresponding to conventional pilocytic astrocytoma in association with NF type 1 [12–14]; these tumors tend to occur at sites where conventional pilocytic astrocytomas are common [1]. In any given single case, however, it may be difficult to decide whether or not features such

as occasional Rosenthal fibers and a limited infiltrative growth pattern are sufficient for a diagnosis of APA in an otherwise typical high-grade astrocytoma. This difficulty is reflected in the variable references to similar findings as either anaplastic/malignant pilocytic astrocytoma or as anaplastic astrocytoma/glioblastoma with Rosenthal fibers [5,15]. Furthermore, in some cases there may be a diagnostic gray zone with respect to pleomorphic xanthoastrocytoma with anaplastic features due to shared morphological findings of Rosenthal fibers and eosinophilic granular bodies, as well as a non-infiltrative growth pattern [16–18].

At present, molecular genetic studies are of limited value for resolving such diagnostic difficulties. While KIAA1549/BRAF fusion products are highly specific for pilocytic astrocytoma, they are only found in small fractions of supratentorial and adult pilocytic astrocytomas [19]. Conversely, the presence of an IDH1 mutation links rare tumors that could morphologically be regarded as APA with the group of diffusely infiltrating gliomas, although its absence does not rule out a conventional high-grade astrocytoma [3].

Loss of PTEN and p16 tumor suppressor genes was reported in APA but not conventional pilocytic astrocytoma, but does not enable distinction from other high-grade gliomas [5].

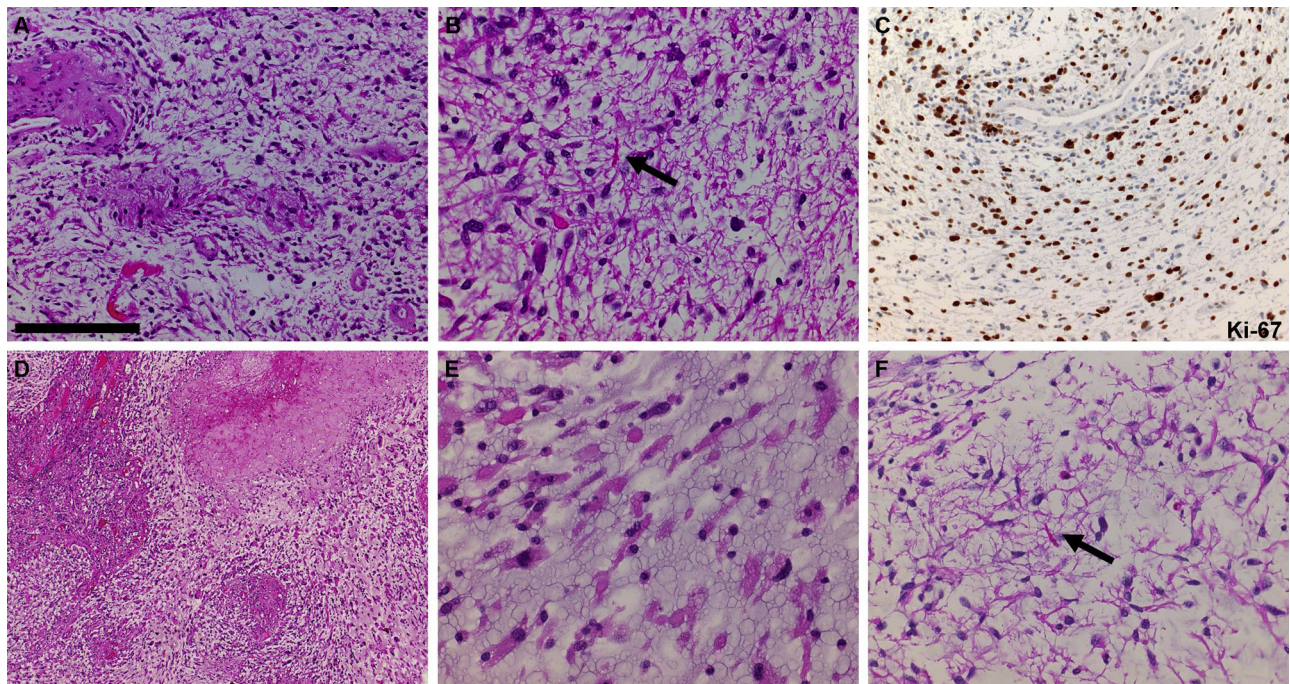


Fig. 2. Histopathological features of anaplastic pilocytic astrocytomas. At medium-power magnification, a characteristic biphasic growth pattern was evident (A, original magnification 200 \times , case 3). Tumor cells show plump, bipolar processes, and rare Rosenthal fibers (arrow) (B, original magnification 400 \times , case 3). Strong nuclear p53 accumulation indicates the presence of a TP53 mutation (C, original magnification 200 \times , case 3). Low-power magnification illustrates biphasic growth pattern and geographic necrosis (D, original magnification 50 \times , case 1). Higher magnification reveals bipolar tumor cells in a myxoid background (E, original magnification 400 \times , case 1). Rare Rosenthal fibers (arrow) (F, original magnification 400 \times , case 2) were identified. Scale bar in (A) corresponds to 50 μ m (B,E,F), 100 μ m (A,C), and 400 μ m (D).

Table 1

Reported cases of anaplastic pilocytic astrocytoma in adults by anatomical region.

Author & Year	Age (yrs), Sex	Location
Ishii et al. 1998 [29]	38, female	Cerebellum
Endo et al. 2003 [30]	70, female	Cerebellum
Shinoura et al. 2006 [31]	70, female	Cerebellum
Stuer et al. 2007 [10]	Not specified	Cerebellum
Azad et al. 2009 [11]	54, female	Cerebellum
Tsuda et al. 2011 [26]	70, female	Cerebellum
Shibahara et al. 2011 [32]	21, male	Cerebellum
Hsieh et al. 2012 [25]	47, female	Cerebellum
Yeo et al. 2013 [33]	36, male	Cerebellum
Yong et al. 2014 [9]	42, female	Cerebellum
Yong et al. 2014 [9]	40, female	Cerebellum
Hitotsumatsu et al. 1994 [6]	30, male	Frontal lobe
Kraus et al. 2000 [34]	46, female	Temporal/parietal lobe
Yong et al. 2014 [9]	33, male	Insular cortex
Current series (case 1)	52, male	Parietal lobe (precuneus)
Current series (case 3)	60, female	Thalamus, insula, temporal lobe
Burkhard et al. 2003 [4]	Not specified	2 cases (not specified)
Theeler et al. 2014 [2]	Not specified	2 cases (not specified) and 1 case with malignant transformation after radiotherapy
Rodriguez et al. 2010, 2011 [1,5]	35 (median age 35, 21 males, 13 females)	34 cases (35% supra-, 65% infratentorial) ^a
Patt et al. 1994 [7]	20, male	Optic nerve
Stuer et al. 2007 [10]	Not specified	Medulla spinalis
Azad et al. 2009 [11]	47, male	Medulla oblongata
Current series (case 2)	41, male	Pons

^aIncludes 10 definite cases of APA (the remaining 24 cases arose from malignant transformation of pilocytic astrocytoma) and an unspecified number of subjects younger than 18 years (range 5–75 years).

The current World Health Organization (WHO) classification of tumors of the central nervous system makes brief mention of malignant transformation of preexisting pilocytic astrocytomas, but otherwise does not provide diagnostic or grading criteria for APA [20]. Importantly, criteria for anaplasia may differ from those in conventional astrocytomas [15]. Furthermore, adult pilocytic astrocytoma may be intrinsically more aggressive than childhood tumors even in the absence of histological signs of anaplasia [10].

4.2. Clinical appearance and advanced neuroradiological techniques

From a clinical and radiological point of view, APA frequently represents a diagnostic pitfall. Contrast enhancement is present in a wide spectrum of tumor types ranging from inflammatory/demyelinating lesions to aggressive gliomas [8]. Various patterns of multifocal and regularly or irregularly enhancing lesions

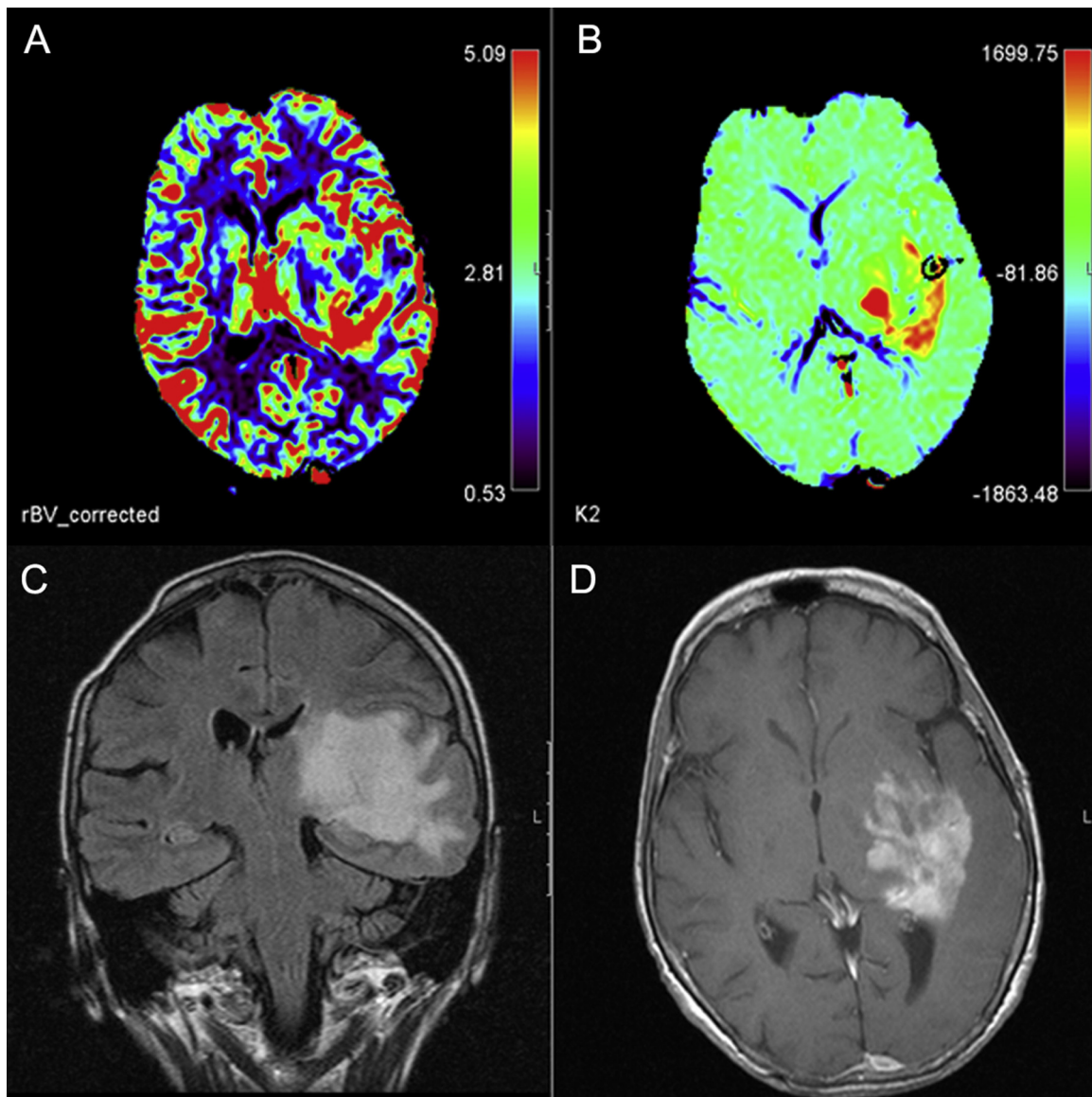


Fig. 3. Magnetic resonance imaging perfusion maps of a patient with anaplastic pilocytic astrocytoma (case 3). Axial relative cerebral blood volume (rCBV) map after leakage correction (A) and K2 leakage map (B). Coronal fluid-attenuated inversion recovery (C) and axial T₁-weighted contrast-enhanced (D) images. The elevated rCBV indicates increased blood flow and vascularization caused by increased angiogenesis within the tumor matrix, which is an indicator of more aggressive behavior.

render the radiological diagnosis challenging [21]. While the use of conventional imaging techniques for prediction of entity and dignity of gliomas is limited, new and advanced neuroimaging techniques such as perfusion imaging and MRI spectroscopy have become increasingly recognized as additive methods to limit the differential diagnosis with regard to tumefactive multiple sclerosis, and low-, or high-grade glioma.

In tumefactive demyelinating lesions perfusion MRI showed reduced relative cerebral blood volume (rCBV) throughout the lesion and magnetic resonance spectroscopy shows slightly elevated Choline (Cho)/Creatin (Cr) and Cho/N-aceylaspartate (NAA) ratios [22]. Reduced rCBV and elevated apparent diffusion coefficient (ADC) values favor low-grade gliomas. Elevated rCBV and cerebral blood flow (CBF) together with reduced ADC and decreased mean transit time (MTT) are suggestive of high-grade gliomas. Furthermore, magnetic resonance spectroscopy in high-grade gliomas typically shows high Cho/Cr and Cho/NAA ratios as well as lactate and mobile lipid resonances resulting from the higher cell membrane turnover as well as anaerobic metabolism and tumor necrosis

[22–24]. In our series, all patients presented with non-specific clinical symptoms together with irregular contrast-enhancing lesions, which initially led to incorrect preoperative diagnoses of malignancy or demyelinating disease (Figs. 3 and 4).

Interestingly, our review of the current literature (Table 1) revealed a tendency for APA to arise in the posterior cranial fossa, which is considered a less common site of adult anaplastic astrocytoma; adult anaplastic astrocytoma occurs predominantly in the cerebral hemispheres. In our series 1 astrocytoma was located in the posterior cranial fossa (case 2) whereas the other cases were atypically situated in the cerebral hemispheres (cases 1 and 3). This observation, namely preferential infratentorial localization, may provide guidance in preoperative differential diagnosis from neuroimaging studies. All patients developed neurological deficits within a few weeks after treatment, which is suggestive of a malignant process. Interestingly, 1 patient (case 3) suffered from NF type 1. This genetic disease was recently mentioned as a potential risk factor for development of APA in addition to its well-established association with WHO grade I pilocytic astrocytomas [25,26].

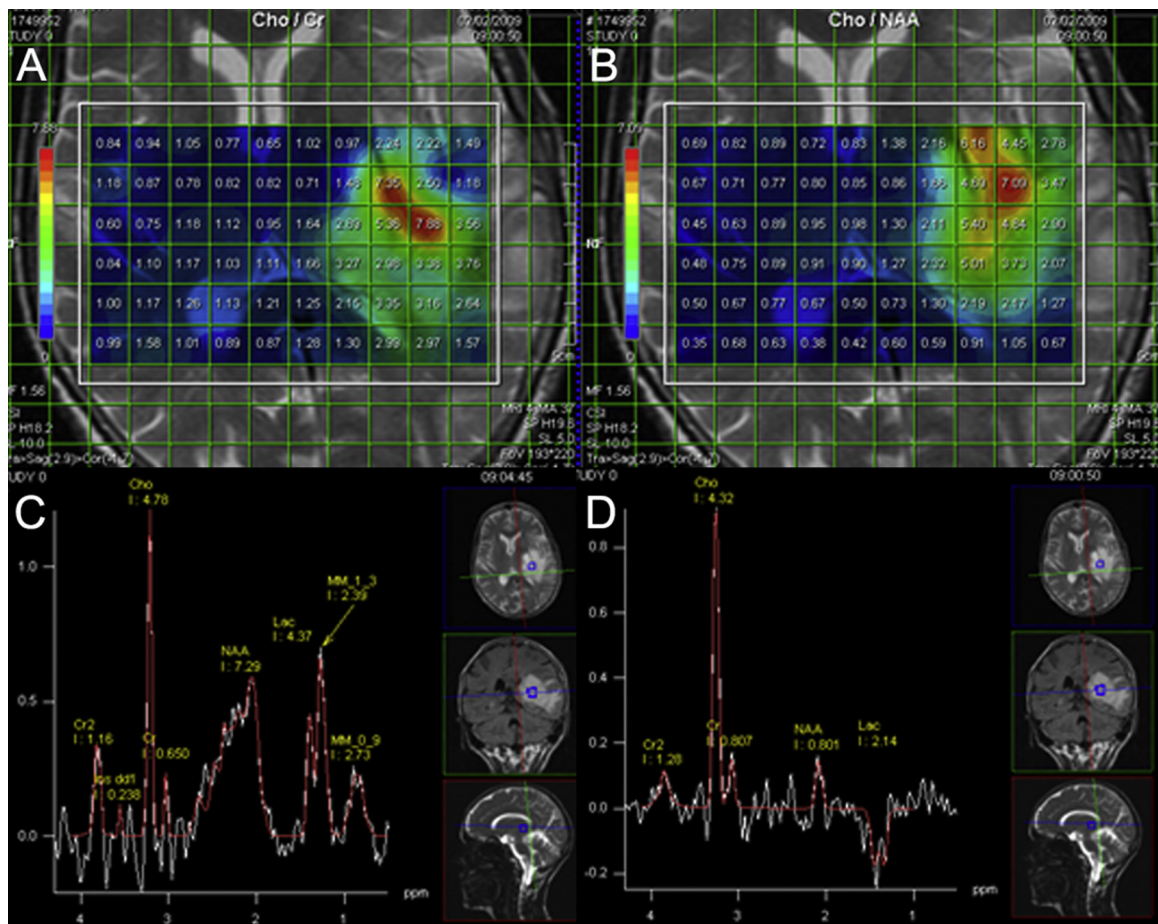


Fig. 4. Magnetic resonance spectroscopy (MRS) of a patient with anaplastic pilocytic astrocytoma (case 3). MRS shows very high Cho/Cr (A) and Cho/NAA (B) ratios in the tumor in the short echo time (TE) chemical shift imaging (CSI) at 30 ms echo time (C), and long TE CSI imaging at 135 echo time (D). At TE = 30 ms CSI reveals a very prominent lactate resonance at 1.33 ppm, asymmetrically displayed because of an overlay with the mobile lipid resonance at 1.3 ppm (C).

Moreover, a recent series reporting 3 cases of adult APA, including 2 patients with NF-1, further emphasized the association of this phakomatosis with APA [9]. However, whether screening for NF-1 in patients diagnosed with APA should be performed as part of the standard clinical workup merits further investigation; in our case series as well as in others a minority of patients had NF-1 [1,3].

4.3. Management, prognostic markers, and outcome

Genetic alterations of IDH1 such as IDH1-R132H, the most frequent IDH1 mutation, are well accepted as prognostic markers in high-grade glioma, with a more favorable outcome in patients with mutated IDH1 [27]. Sugita et al. describe a strong positive staining pattern for IDH1-R132H protein in anaplastic astrocytoma with abundant Rosenthal fibers [3]. However, our cases were all negative for IDH1-R132H staining. In a comprehensive database of pilocytic astrocytomas published by Theeler et al., 2 patients showed malignant transformation after irradiation [2]. A literature review by Parsa et al. attributed this phenomenon to irradiation of pilocytic astrocytoma rather than to spontaneous mutations [28]. Therefore, malignant progression of a pilocytic astrocytoma to APA, or APA as a variant of anaplastic astrocytoma, appears to be very unlikely. This can be confirmed by our series, which presents cases of APA without any previous tumor treatment such as chemotherapy or irradiation prior to histopathological diagnosis.

Concerning management of APA in adults it is presently not feasible to make any general recommendations due to lack of data in the present literature. Our cases were treated by resection

(whenever possible) followed by radiation therapy. However, which role radio-/chemotherapy may play in treatment of APA in adults has to be investigated.

Anaplastic astrocytoma frequently progresses to secondary glioblastoma after a mean interval of 2 years [3]. However, Sugita et al. describe 2 cases (out of four) of anaplastic astrocytoma with abundant Rosenthal fibers that followed a more indolent course than conventional anaplastic astrocytoma [3]. This observation was also confirmed in an earlier study from Burkhard et al. where 2 patients with APA had documented follow-ups of 7 and 10 years [4]. Similarly, we observed prolonged survival of up to 35 months in 1 patient.

5. Conclusion

APA in adults is a very rare, diagnostically challenging, and distinct type of astrocytoma that usually occurs in older patients as compared to conventional pilocytic astrocytoma, but occurs at a younger age with more favorable outcome as compared to pure anaplastic astrocytoma. Further, modern imaging techniques such as MRI perfusion and spectroscopy allow better differentiation of APA from other neurological disease than conventional imaging techniques. We summarized our experience with 3 documented cases of adult APA adding one of the largest case series of APA in the literature, which are even more unusual and unique than juvenile APA. Moreover, we added a first review of the literature to update the reader's knowledge about APA in adults including relevant features in histopathology and modern neuroradiological procedures.

The difficulties in differential diagnosis and management of these uncommon neoplasms might be due to the ability to mimic various neurological pathologies and the lack of distinct molecular markers. Improvements in the care of patients affected by APA may be fostered by increased perception of this entity. Although currently not explicitly recognized as a distinct clinico-pathologic entity it seems that adult APA behave differently from conventional high-grade glioma and should be included in differential diagnostics to enable adequate patient care. Further studies are needed to better understand this extremely rare disease.

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